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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte SATISHCHANDRA P. PATEL

Appeal 2009-002841[1]
Application 10/632,970
Technology Center 1600

Decided: August 28, 2009

Before ERIC GRIMES, LORA M. GREEN, and
FRANCISCO C. PRATS, *Administrative Patent Judges*.

PRATS, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a pharmaceutical composition containing a cyclosporin and a mixture of monoesters and diesters of propylene glycol with fatty acids. The Examiner has rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

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[1] Satishchandra P. Patel is the real party in interest.

We reverse.

STATEMENT OF THE CASE

"The cyclosporins are very lipophilic and hydrophobic compounds, which are sparingly soluble in water, but dissolve readily in organic solvents such as methanol, ethanol, chloroform and the like. The low solubility in water results in extremely low bioavailability of the cyclosporins when administered orally" (Spec. 1).

Because of their low water solubility "[p]rior art formulations of cyclosporins for oral administration have often involved combinations of the cyclosporin with a surfactant, an oil, and a co-surfactant" (*id.*). One prior art composition combines cyclosporin with "propylene glycol monoesters of C_6-C_{18} fatty acids. The monoester content employed is typically >90%, and usually 100%" (*id.*).

The Specification discloses a carrier medium for cyclosporins with a mixture of specific fatty acid monoesters and diesters of propylene glycol that results in a "a particularly good solvent medium for cyclosporins, and therefore it is possible to avoid co-solvents such as ethanol, propylene glycol, or the like. The compositions according to the present invention accordingly preferably do not have such co-solvents, and in particular preferably do not contain ethanol" (*id.* at 5).

Claims 1 and 4-20 are pending and on appeal (App. Br. 2-3). Claim 1, the only independent claim, is representative and reads as follows:

> 1. A pharmaceutical composition suitable for oral administration in the form of a homogeneous solution which on exposure to water or gastrointestinal fluids forms an emulsion having a particle size of less than 5 microns, the solution comprising: (a) a pharmaceutically effective amount of a cyclosporin, (b) a carrier medium comprising a mixture of

> mono- and diesters of propylene glycol with fatty acids having from 8 to 10 carbon atoms or with mixtures of such fatty acids, wherein the monoester makes up between 50 and 60 mol % of the mixture, and (c) a non-ionic surfactant having a hydrophilic lipophilic balance (HLB) greater than 10.

The Examiner cites the following document as evidence of unpatentability:

Mulye	WO 00/33862 A1	Jun. 15, 2000

Claims 1 and 4-20 stand rejected under 35 U.S.C. § 103(a) as being obvious in view of Mulye (Ans. 3-4).

OBVIOUSNESS

ISSUE

The Examiner cites Mulye as disclosing a self-emulsifying composition containing all of the claimed ingredients, except that "Mulye does not explicitly teach mixture[s] of mono- and diester propylene glycol" (Ans. 3). The Examiner finds, however, that "Mulye teaches [a] mixture of fatty acids contain[ing] 60% of monoester propylene glycol (page 16), and . . . only exclude[s] the presen[ce] of triglycerides" (*id.* at 4). Based on these teachings, the Examiner concludes that "it would have been obvious to one of ordinary skill in the art to include diester propylene glycol in the mixture, because Mulye does not exclude the use of diester propylene glycol" (*id.* at 3).

Appellant contends, among other things, that "Mulye points out, time and time again, that the [propylene glycol] monoester must be at least about 60% by weight, an amount which when translated into mole % is in excess of 70 m[ol]%" (App. Br. 8). In contrast, Appellant argues, claim 1 requires

"the monoester [to be] less than 60 mole percent of the monoester/diester mixture" (*id.* at 7).

Appellant urges that "by virtue of the presence of the second ester moiety, the diester is heavier than the monoester, and therefore, 60 mole percent [as recited in claim 1] will be substantially less than [the] 60% monoester on a weight basis" disclosed by Mulye as being the minimum amount of monoester (*id.*). Specifically, Appellant calculates that a "60 mole % content of the propylene glycol monoester of the C_8 fatty acid in a mixture with propylene glycol C_8 fatty acid diester corresponds to 48 weight percent; and the corresponding conversions into weight percents for the C_9 and C_{10} fatty acid monoesters are lower than for the C_8 fatty acid" (*id.* (footnote omitted)).

In performing the calculation, Appellant reasons that "60 moles of mono-C_8 ester of propylene glycol (mol. wt. = 202) weighs 12120 and 40 moles of diester (mol. wt. = 328) weighs 13120; [a]ccordingly, weight percent = 100(12120/12120 + 13120) = 48 wt% monoester" (*id.*, n. 1). Therefore, Appellant finds, when comparing Mulye and claim 1 on a weight percentage basis of the propylene glycol esters, Mulye requires "at least 'about' 60 wt% monoester (or 58% and higher according to the Examiner) while the invention uses less than 50 wt%" (*id.*).

Appellant further contends that this difference between claim 1 and Mulye cannot be considered obvious based on an optimization rationale (*id.* at 8-9). Specifically, Appellant argues, Mulye's comparative examples demonstrate that "the composition must contain more than about 60 wt% monoester in order to be storage stable and non-hydroscopic [sic, hygroscopic], and thus teaches the skilled person that a composition in

which the monoester is less that about 60% by weight will not be storage stable and will be hydroscopic [sic]" (*id.* at 8).

In view of the positions advanced by Appellant and the Examiner, the issue with respect to this rejection is whether Appellant has shown that the Examiner failed to make a prima facie case that an ordinary artisan viewing the teachings of Mulye would have considered it obvious to include a mixture of mono- and diesters of propylene glycol with fatty acids having from 8 to 10 carbon atoms or with mixtures of such fatty acids, wherein the monoester makes up between 50 and 60 mol % of the mixture, in Mulye's cyclosporin compositions.

FINDINGS OF FACT ("FF")

1. Mulye states:

> The present invention is . . . directed to a method of orally administering a pharmaceutical composition containing a lipophilic drug to a patient in need thereof, comprising orally administering to said patient a pharmaceutical composition comprising a pharmaceutically effective amount of a lipophilic drug, a drug solubilizing effective amount of a propylene glycol ester of C_6-C_{18} fatty acid with at least 60% by weight monoester based on the total weight of the propylene glycol and a sufficient amount of a non-ionic surfactant having a HLB greater than 10, said surfactant being present in sufficient amounts to form a microemulsion with said lipophilic drug and said propylene glycol ester when brought in contact with an aqueous medium, e.g. water.

(Mulye 9.)

2. Mulye states that the "most preferred drugs are cyclosporin and ibuprofen" (*id.* at 13). Mulye further states that "it is preferred that the fatty acid of the propylene glycol monoester contains 6-16 carbon atoms, and

more preferably 8-12 carbon atoms, and most preferably 8-10 carbon atoms, and even more preferably 8 or 10 carbon atoms" (*id.* at 15).

3. Regarding the propylene glycol ester component of its compositions, Mulye states:

> The second component, as indicated hereinabove, is a lipid fatty acid esterified product of propylene glycol containing at least about 60% monoester based on the total weight of propylene glycol ester, i.e., only one of the hydroxy groups is esterified. The term "ester of propylene glycol containing at least about 60% monoester by weight" signifies that at least about 60% by weight up to a maximum of 100% of the esters formed in the esterification reaction is the monoester. Although the second component may contain any amount of monoester above the 60% level based on the total weight of the propylene glycol ester, including 60%-100% inclusive, e.g. including at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98% or 99% by weight, it is preferred that the propylene glycol ester contains at least about 70% by weight monoester, and most preferably at least about 90% by weight monoester. However, in a preferred embodiment, it contains at least about 95% by weight monoester and in another preferred embodiment, at least about 99% by weight monoester.

(*Id.* at 16.)

4. In Example 8, Mulye performed a comparison between cyclosporin compositions having different amounts of propylene glycol-caprylate (eight carbon fatty acid) monoesters (*id.* at 33). The results are presented in the following table:

EXAMPLE	FORMULATION	INITIAL OBSERVATION	OBSERVATION AFTER 1 MONTH
Comparative Example 1	Cyclosporin 100mg Propylene glycol Dicaprate Caprylate, Diester>90% Polyoxyl 35 Castor oil (Cremophore EL 35) 300mg	Clear	Precipitation and Crystallization (after 1 week)
Comparative Example 2	Cyclosporin 100mg Propylene glycol Laurate, Monoester about 45 to 55% 200mg Polyoxyl 35 Castor oil (Cremophore EL 35) 300mg	Clear	Precipitation and crystal growth (after 2 weeks)
Example 8	Cyclosporin 100mg Propylene glycol mono-Caprylate, Monoester >80% 200mg Polyoxyl 35 Castor oil (Cremophore EL 35) 300mg	Clear	Clear solution after more than 1 months

(*Id.*)

5. The Examiner does not dispute the accuracy of Appellant's calculation (App. Br. 7) that the upper limit of 60 mole % propylene glycol monoester in claim 1 converts to 48% monoester by weight.

6. The Examiner does not dispute the accuracy of Appellant's assertion (App. Br. 8) that Mulye's lower limit of 60 weight % propylene glycol converts to greater than 70 mole %.

PRINCIPLES OF LAW

> In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. "[The Examiner] can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references."

In re Fritch, 972 F.2d 1260, 1265 (Fed. Cir. 1992) (citations omitted, bracketed material in original). Furthermore, "[e]ven when obviousness is based on a single prior art reference, there must be a showing of a suggestion or motivation to modify the teachings of that reference." *In re Kotzab*, 217 F.3d 1365, 1370 (Fed. Cir. 2000).

In *KSR Int' l Co. v. Teleflex Inc.*, 550 U.S. 398, 415 (2007), the Supreme Court emphasized "an expansive and flexible approach" to the obviousness question. However, the Court nonetheless reaffirmed that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *Id.* at 418.

Rather, as the Court stated:

> [I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements *in the way the claimed new invention does* . . . because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.

Id. at 418-419 (emphasis added); *see also id.* at 418 (requiring a determination of "whether there was an apparent reason to combine the known elements *in the fashion claimed* by the patent at issue") (emphasis added).

With respect to the obviousness of ranges, our reviewing court has stated that "the discovery of an optimum value of a variable in a known process is usually obvious." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1368 (Fed. Cir. 2007). The rationale for determining the optimal parameters for prior art result effective variables "flows from the 'normal desire of scientists or artisans to improve upon what is already generally known.'" *Id.* (quoting *In re Peterson,* 315 F.3d 1325, 1330 (Fed. Cir. 2003)).

The Federal Circuit has also stated that, "[i]n cases involving overlapping ranges, we and our predecessor court have consistently held that even a slight overlap in range establishes a *prima facie* case of obviousness."

Peterson, 315 F.3d at 1329. Moreover, "a *prima facie* case of obviousness exists when the claimed range and the prior art range do not overlap but are close enough such that one skilled in the art would have expected them to have the same properties." *Id.*

Once a prima facie case of obviousness based on overlapping or close ranges has been established, however, "an applicant may rebut [the] *prima facie* case of obviousness by showing that the prior art teaches away from the claimed invention in any material respect." *Id.* at 1331.

ANALYSIS

We agree with Appellant that the Examiner failed to make a prima facie case of obviousness. The Examiner argues that claim 1 does not recite a limitation that differentiates the claimed amounts of propylene glycol monoesters from the amounts in Mulye's compositions (Ans. 4). Specifically, the Examiner urges that "the feature upon which applicant relies (i.e., less than 50% monoester) is not recited in the rejected claims" (*id.*).

We are not persuaded. Claim 1 recites a composition that has "a mixture of mono- and diesters of propylene glycol with fatty acids having from 8 to 10 carbon atoms or with mixtures of such fatty acids, wherein the monoester makes up between 50 and 60 *mol %* of the mixture" (emphasis added).

As Appellant points out, and the Examiner does not dispute, the claimed upper limit of 60 mole percent equates to 48 percent by weight (FF 5). In contrast, Mulye discloses that the lower limit of the corresponding ingredient in its compositions is "at least about" 60 percent by weight, with much greater percentages being preferred (FF 3).

Even in view of the "about" language in Mulye, we do not agree with the Examiner that an ordinary artisan would consider Mulye's requirement of at least about 60 percent monoester by weight to suggest the claimed amount, which must be less than 48 percent by weight. Moreover, even if Mulye's weight percentage is converted to mole percent, Mulye's undisputed *lower* limit of 70 mole percent (FF 6) is significantly higher than the claimed *upper* limit of 60 mole percent.

Nor do we agree with the Examiner that an ordinary artisan following Mulye's teachings would have arrived at the claimed monoester percentage through optimization. First, the range recited in claim 1 cannot be said to overlap, or even abut the range disclosed by Mulye. *See In re Peterson,* 315 F.3d at 1329.

Also, Mulye shows, through comparative examples, that reducing the monoester content of the propylene glycol component to about 45 to 50 weight percent of monoesters of lauric acid (twelve carbon fatty acid) yields a cyclosporin composition that precipitates and crystallizes after two weeks (FF 4). Thus, we do not agree that a person of ordinary skill in the art seeking to optimize Mulye's compositions would have done so by reducing the monoester content of the propylene glycol component below the lower limit described by Mulye.

In sum, for the reasons discussed, we agree with Appellant that the Examiner failed to make a prima facie case that an ordinary artisan viewing the teachings of Mulye would have considered it obvious to include a mixture of mono- and diesters of propylene glycol with fatty acids having from 8 to 10 carbon atoms or with mixtures of such fatty acids, wherein the monoester makes up between 50 and 60 mol % of the mixture, in Mulye's

cyclosporin compositions. We therefore reverse the Examiner's rejection of claim 1 and its dependent claims as being obvious over Mulye.

REVERSED

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